Deadly infectious diseases such as Ebola: the parachute paradigm

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The management of patients suffering from deadly diseases without known treatment poses questions that challenge the sacrosanct recommendation for randomized controlled trials. When a disease has a mortality rate close to 40% (as for the ongoing Ebola outbreak) and when a potential treatment exists, is it reasonable to design a preliminary simple and brief study to observe a decrease of mortality rate of 50%, needing to include only 40 individuals, compared with a retrospective study. This query emerged a few years ago, but recommendations supported blindly by evidence-based medicine have become the rule. Recommendations considered to be the best are those that are based on at least two double-blind randomized studies performed by two independent scientific teams. This was particularly used in oncology and cardiovascular diseases, where studies can easily include a large number of patients with stereotypical clinical involvement. The application of such studies in infectious diseases remains hazardous.

First, it is very complex to randomize infected patients from different countries for several clinical syndromes such as meningitis or pneumonia. Indeed, infectious diseases are frequently associated with specific ecosystems and consequently the treatments that seem suitable in some parts of the world are not effective in other regions. As an example—the main cause of blood-culture-negative endocarditis after surgery in western countries, as investigated using molecular tools, is *Streptococcus* spp. whereas in Thailand a zoonotic causative bacterium is usually involved (*Coxiella burnetii*, *Bartonella* spp., *Streptococcus suis*) [1,2]. Consequently, the results from randomized controlled trials performed in western countries could not be effectively applied in southern countries. Indeed, the epidemiology of infectious disease resists globalization.

Regarding deadly diseases, the problem of evaluating Ebola therapies was comprehensively illustrated by the parachute paradigm, published in 2003 in the *British Medical Journal*. The authors performed a meta-analysis on the use of a parachute after gravitational challenge and observed, not surprisingly, that no randomized controlled trials of parachute use had been published [3]! Consequently, the authors proposed that those individuals who insist that all interventions need to be validated by a double-blind randomized controlled trial be included in a study where they are equipped with a bag with or without parachute and undergo a gravitational challenge. Strangely, it seems that the authors have failed to include enough volunteers! In addition, what would be the opinion of an ethics committee?

Recently, part of the science community, mainly composed of the more rigorous methodologists, denounced that randomized controlled trials of Ebola management had not been proposed to seriously evaluate therapeutic management [4]. In parallel, we observed that all the healthcare workers from western countries infected with Ebola had received, after repatriation, the best available supporting care plus all the available experimental treatments but were never evaluated. Would it be ethical to oppose for western healthcare workers a strategy based on "any medical solution to avoid death", while for African individuals we would propose randomized clinical trials? In deadly clinical situations, we should forget methodology to return to previous practices, that of the tyranny of the evidence. Compassionate treatment should be largely proposed in such a situation. In addition, the expert opinions of the clinicians who have managed several tens or hundreds of patients, in contrast to those of specialists in expertise, should not be overlooked [5].

References

[1] Fournier PE, Thuny F, Richet H, Lepidi H, Casalta JP, Arzouni JP, et al. Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. Clin Infect Dis 2010;51:131–40.

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[2] Watt G, Pachirat O, Baggett HC, Maloney SA, Lulitanond V, Raoult D, et al. Infective endocarditis in northeastern Thailand. Emerg Infect Dis 2014;20:473–6.

[3] Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ 2003;327(7429):1459–61.

[4] Cox E, Borio L, Temple R. Evaluating Ebola therapies–the case for RCTs. N Engl J Med 2014;371:2350–1.

[5] Raoult D. Chronic Q fever: expert opinion versus literature analysis and consensus. J Infect 2012;65:102–8.